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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/781,142	02/18/2004	Stephanos Kyrkanides	24376.31.8401	3987

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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
05/10/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

agg.patent.docketing@agg.com

Office Action Summary	Application No.	Applicant(s)	
	10/781,142	KYRKANIDES, STEPHANOS	
	Examiner	Art Unit	
	JOANNE HAMA	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *44-71,76-82 and 92-132* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13,16-21,23-28,31-43,72-74,87,90,91,134 and 135* is/are rejected.

7)☒ Claim(s) *14,138 and 142* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-11,13,14,16-21,23-28,31-74,76-82,87,90-132,134,135,138 and 142.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 8, 2010 has been entered.

Applicant filed amendments to the claims on January 8, 2010. Claims 1, 22, 29, 30, 110 are amended. Claims 12, 15, 75, 84-86, 88, 89, 133, 136, 139-141, 143 are cancelled. Claims 44-71, 76-82, 92-132 are withdrawn.

It is noted that Applicant must use the appropriate status identifiers for the claims or risk non-entry of the amendments. See 37 CFR 1.121. It is noted that Applicant has amended claims 1, 110 and has indicated the claims as "previously presented" or "withdrawn." The status identifiers for these claims are "currently amended" and "withdrawn, currently amended."

Claims 1-11, 13, 14, 16-43, 72-74, 83, 87, 90, 91, 134, 135, 138, 142, drawn to a composition comprising an isolated nucleic acid comprising a Hex-alpha and Hex-beta sequence, and to a method of making said composition

Withdrawn Rejections

35 USC § 112, 1st parag., Written Description

Applicant's arguments, see pages 16-22 of Applicant's response, filed January 8, 2010, with respect to the rejection of claims 1, 4, 6, 16-18, 25 as lacking written description have been fully considered and are persuasive. Applicant indicates that the specification teaches "parts of these promoters can be fused together to, for example, produce a CMV-beta actin fusion promoter, such as the one shown in SEQ ID NO. 23 (Applicant's response, page 21). In a search of SEQ ID NO. 23, the sequence is identified as a CMV enhancer/beta-actin promoter. As such, the term "promoter" encompasses the use of an enhancer. The rejection of claims 1, 4, 6, 16-18, 25 has been withdrawn.

35 USC § 112, 1st parag., Enablement

Applicant's arguments, see pages 22-23 of Applicant's response, filed January 8, 2010, with respect to the rejection of claims 1, 4, 6, 16-18, 25, 26, 29, 30, 87, 89 as lacking enablement have been fully considered and are persuasive. Applicant indicates that the specification teaches "parts of these promoters can be fused together to, for example, produce a CMV-beta actin fusion promoter, such as the one shown in SEQ ID NO. 23 (Applicant's response, page 21). In a search of SEQ ID NO. 23, the sequence is identified as a CMV enhancer/beta-actin promoter. As such, the term "promoter" encompasses the use of an enhancer. The rejection of claims 1, 4, 6, 16-18, 25, 26 is withdrawn with regard to this aspect of the rejection.

With regard to the claims being drawn to HEXB product cross-correcting and catabolizing GM2 gangliosides (claims 29, 30), Applicant has amended

claims 29, 30 to depend on claim 27 (Applicant's response, page 23). This is persuasive and the rejection as it applies to these claims is withdrawn.

With regard to the rejection of claim 89, Applicant indicates that the claim has been cancelled (Applicant's response, page 23). This is persuasive and the rejection as it applies to this claim is withdrawn.

It is noted that while claim 87 is rejected, this appears to be a typographical error and should be a rejection of claim 88. It is noted that claim 87 is rejection under 103, see below. The rejection of claim 88 is withdrawn as the claim is cancelled (see claims filed February 9, 2009).

35 USC § 112, 2nd parag.

Applicant's arguments, see page 23 of Applicant's response, filed January 8, 2010, with respect to the rejection of claims 22, 89 have been fully considered and are persuasive. Applicant indicates that claim 22 is amended to depend from claim 20 and claim 89 has been cancelled. The rejection of claims 20, 89 has been withdrawn.

New/Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11,13, 16-21, 23, 24, 26-28, 31-39, 43, 72-74, 134, 135 remain rejected and claim 25 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Brown and Mahuran, 1993, American Journal of Human Genetics, 53: 497-508, in view of Li and Li, 2001, International Congress Series, 1223: 3-15, Rossi et al., 1998, Nature Genetics, 20: 389-393, Kim et al., 1992, Molecular and Cellular Biology, 12: 3636-3643, Proia, 1988, PNAS, USA, 85: 1883-1887, Myerowitz et al., 1985, PNAS, USA, 82: 7830-7834, Patapoutian et al., WO 02/101045 A2, published December 19, 2002, Hobbs [online], 1997 [retrieved on 2008-03-02]. Retrieved from the Internet:< URL: http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?cmd=Retrieve&db=Nucleotide&list_uids=2329859&dopt=GenBank&WebEnv=0npmzO46M-ZDooSlRrzuukhPw99ul5bvKx98CayPdO_uLYe5w4_-6eC9cd-KucPViMuvowjZ0gwTJT%40256362576FC165A0_0107SID&WebEnvRq=1>, pages 1-3, Hennighausen and Fleckenstein, 1986, EMBO Journal, 5: 1367-1371, Kost et al., 1983, Nucleic Acids Research, 11: 8287-8301, Kistner et al., 1996, PNAS, USA, 93: 10933-10938, Sauer, 1998, Methods, 14: 381-392, Banerjee et al., 1994, The Journal of Biological Chemistry, 269: 4819-4826, Niwa et al., 1991, Gene, 108: 193-200, for reasons of record, March 26, 2008, July 8, 2009.

With regard to the rejection of claim 25, Niwa et al. teach a promoter that comprises the CMV-IE enhancer sequence with that of the chicken beta-actin promoter and that this composite promoter produced the highest levels of beta-Gal expression in all the 4 cell lines tested (Niwa et al., abstract; page 194, 1st col. under a) Promoter selection). As such, given this teaching, an artisan would

have used the CMV enhancer/beta-actin promoter because it expresses a gene of interest at high levels. An artisan would have also used it because it is a functional equivalent of a constitutively active promoter such as those taught by Brown and Mahuran (SV40 late promoter, Office Action, March 26, 2008, page 8), Hennighausen and Fleckenstein (CMV promoter, Office Action, March 26, 2008, page 10), and Kost et al., (beta-actin, Office Action, March 26, 2008, page 10). Using one constitutive promoter over the other is a matter of design choice.

Applicant's arguments filed January 8, 2010 have been fully considered but they are not persuasive.

Applicant refers to Takeda Chem. Indus., Ltd. V. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Circ. 2007), wherein the Federal Circuit in Takeda found claims to compound non-obvious over the close "lead compound" prior art, which differed by mere atoms, because the skilled artisan would not be led to modify the closest compound for the property, the unclaimed property, providing a specific utility for the compounds. The closest compounds were found to have the specific property of antidiabetic activity, which was not recited in the claims. Applicant indicates that the Office Action finds the two plasmid system of Brown and Mahuran the "closest "compound," the question becomes would one be motivated with a reasonable expectation of success to modify these "compounds" as disclosed in Mahuran to arrive at the claimed compound. The Action asserts that Kim et al. provides the missing element of a single plasmid having a linking sequence. Applicant argues that Kim et al. do not provide the specific motivation and expectation of success because of a specific requirement

of GM2 catabolism (Applicant's emphasis, Applicant's response, pages 24-25). In response, this is not persuasive. With regard to Applicant indicating that Kim does not provide the motivation and expectation of success of GM2 catabolism, Applicant is correct. The Examiner relied on Brown and Mahuran for teaching that HEX A catabolizes GM2. Brown and Mahuran teach that when two expression vectors (one comprising the coding sequence of HEX-alpha and the other comprising the coding sequence of HEX-beta) expressed Hex-alpha and Hex-beta protein, the alpha and beta units dimerize to form HEX A. HEX A activity was determined by measuring the amount of MUGS substrate was processed. It is noted that HEX A hydrolyzes GM2 ganglioside and that MUGS is an artificial substrate that is used to measure HEX A's ability to catabolize GM2 ganglioside (Sigma [online], 2010 [retrieved on 2010-05/04]. Retrieved from the Internet:
<URL:http://www.sigmaaldrich.com/etc/medialib/docs/Sigma/Product_Information_Sheet/2/m0662pis.Par.0001.File.tmp/m0662pis.pdf>, page 1). Given this teaching, an artisan would know that processing of MUGS is indicative that HEX A heterodimer is present and that the heterodimer is biologically active. Kim et al. was cited to teach that expressing two genes of interest from one expression construct is routine. As such, an artisan would have combined Brown and Mahuran with that of Kim et al. in order to arrive at an expression system that expressed Hex-alpha and Hex-beta, wherein when Hex-alpha and Hex-beta proteins dimerize to form HEX A, wherein HEX A catabolizes GM2 ganglioside. In addition to Brown and Mahuran teaching that HEX A catabolizes GM2

gangliosied, Chavany and Jendoubi, 1998, Molecular Medicine Today, 4: 158-165, teach that HEX B is a homodimer of beta subunits and has similar substrate specificity to HEX A with the key exception that it does not hydrolyze GM2 (Chavany and Jendoubi, page 158, 2nd col., 1st parag.). Finally, even if the art did not specifically disclose that HEX A heterodimer has the ability to catabolize GM2 ganglioside, it is noted that the HEX A heterodimer formed by expressing Hex-alpha and Hex-beta would have had this ability. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

Applicant indicates the Office Action indicates that there is a reasonable expectation of success that an artisan would have made the expression vector because Kim et al. teach that the expression system expresses two or more transgenes spatially and temporally in one cell (Office Action, page 12). The Office Action misapplies the standard of reasonable expectation of success. Applicant indicates that reasonable expectation of success has been applied incorrectly, as reasonable expectation of success is filtered through the predictability of the invention, which is defined by the claims. It is not obvious to arrive at the claimed composition, wherein the HEX-beta and HEX-alpha can form a dimer and wherein the dimer catabolizes GM2 ganglioside (Applicant's response, pages 25-26). In response, this is not persuasive. While Applicant indicates that reasonable expectation of success is applied to the expectation

that a dimer of Hex-beta and Hex-alpha is formed, this expectation of success is incorrectly applied. Reasonable expectation of success is applied to whether or not an artisan would have arrived at the claimed invention of an expression vector that comprises the coding sequences of Hex-beta and Hex-alpha. With regard to Applicant indicating whether there is predictable expectation of success of the two expressed proteins dimerizing and having a particular biological activity, it is noted that Brown and Mahuran and Chavany and Jendoubi teach that Hex-alpha/Hex-beta dimers catabolize G2M ganglioside. Further, as discussed above, even if the art was unaware of whether the HEX A dimer was able to catabolize GM2, the ability for the dimer to do so is inherent.

Applicant indicates the limitation, wherein Hex-beta and Hex-alpha can form a dimer and wherein the dimer can catabolize GM2 ganglioside in vivo, was not given credence to this limitation. The limitation brings into play the purpose of making the claimed composition. Guidotti et al., 1999, teach that this limitation is non-functional (in vivo). Guidotti et al. teach that the construct of Brown and Mahuran does not form the functional dimer in vivo (Applicant's response, page 23). In response, this is not persuasive. Guidotti et al. teach compared to hexa-/- mice that received only AdHEXA, hexa-/- mice given AdHEXA and AdHEXB resulted in high HexA activity in the liver (9-fold more than the normal value) and in partial or total correction in other tissues (heart, skeletal muscle, spleen, and kidney) (Guidotti et al., page 832, 2nd col., 2nd and 3rd parag.). As such, this is teaching that HEX A heterodimer is formed and is active.

Applicant indicates that the claims are limited to a specific orientation, through the limitation of having GM2 catabolization in vivo because in a bicistronic vector, there is a single orientation which achieves this limitation. It would not be obvious as asserted by the Office Action to arrive at the claimed invention because the art taught by the Examiner teaches a genus of bicistronic vectors, not the subset of bicistronic vectors, as claimed (Applicant's response, page 27). In response, this is not persuasive. The claims are drawn to bicistronic (i.e., two genes of interest that are expressed) and there are only two orientations for a bicistronic gene. It could either be gene a, an IRES, and gene b; or gene b, an IRES, and gene a. It would have been obvious for an artisan to arrive at two orientations of the construct.

Thus, the claims remain rejected.

Claims 1, 4, 6, 39-42, 87, 90, 91 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Brown and Mahuran, 1993, American Journal of Human Genetics, 53: 497-508, in view of Li and Li, 2001, International Congress Series, 1223: 3-15, Kim et al., 1992, Molecular and Cellular Biology, 12: 3636-3643, Chavany and Jendoubi, 1998, Molecular Medicine Today, 4: 158-165, Schuette et al., 1999, Biol. Chem. 380: 759-766, Litchtler et al., 1989, The Journal of Biological Chemistry, 264: 3072-3077, Klimatcheva et al., 1999, Frontiers in Bioscience, 4: 481-496, for reasons of record, March 26, 2008, July 8, 2009.

It is noted that Applicant provides no arguments regard the rejection of these claims. As such, the rejection as it applies to these claims remains.

Conclusion

Claims 14, 138, 142 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 83 is allowable.

Claims 1-11, 13, 16-43, 72-74, 87, 89-91, 134 and 135 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Tuesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Joanne Hama/
Primary Examiner
Art Unit 1632